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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,553	EATON ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10 September 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 9 September 2002 has been entered. Claims 1 – 13 are under examination in the instant office action.

Priority

The preliminary amendment filed 9 September 2002 indicates that this application is a continuation of application 10/006867, which is a continuation of PCT/US00/23328, which is a continuation-in-part of application 09/390137. The instant disclosure receives priority to 24 August 2000, the earliest application in which the specification was identical. Priority is not granted to earlier applications because the disclosure is not enabling.

It is noted that applicants may argue that the results of the assay beginning on page 140 (paragraph 529) of the specification, the Tumor versus Normal Differential Tissue Expression Distribution assay, establish utility and enablement for the claimed invention, resulting in an earlier priority date. That assay is found to be lacking utility and therefore is not found to be enabling as required by 35 U.S.C. § 112, first paragraph for reasons described below in the rejections under 35 U.S.C. §§ 101 and 112, below.

Information Disclosure Statement

The information disclosure statement filed 17 September 2002 has been considered. The BLAST results demonstrate that applicants are aware of nucleic acids with identity or homology to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the examiner cannot determine if said sequences constitute prior art.

U.S. Patent 5,546,637 is cited on the information disclosure statement as being issued to Jacobs et al. on 16 July 1997. However this patent was issued to Niedecker on 20 August 1996. The patent has been considered but it is not immediately obvious how the subject matter contained therein is related to the instant application. Note that the '637 patent is to a device to close sausages.

Specification

The disclosure is objected to because of the following informalities:

The title is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The specification includes browser-executable hyperlinks. This objection could be overcome by deleting all occurrences of the text "http://".

Appropriate correction is required.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 – 13 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The claims are drawn to isolated polypeptides called PRO994, variants at least 80% identical to same, fragments of same, and chimeric polypeptides.

The specification discloses, on pp. 140 – 144, the results of an assay in which certain cDNA molecules showed differential expression in tumor tissue versus control tissue. The results indicate that DNA58855-1422, which encodes PRO994 (see specification p. 15, paragraph 73) is more highly expressed in normal stomach than in stomach tumor, and is more highly expressed in rectum tumor than in normal rectum. The specification (p. 140, paragraph 530) asserts that a nucleic acid molecule differentially expressed in normal as compared to tumor cells of the same tissue is useful as a diagnostic to determine the presence or absence of a tumor. The specification also asserts that nucleic acids differentially expressed in tumors are useful as therapeutic targets for the treatment of tumors. The asserted utility in diagnosis and treatment is not substantial for the following reasons. First, it is unclear whether the changes in expression of the PRO994-encoding cDNA is statistically significant, and whether such changes in the expression of the cDNA are correlated with changes in expression of the encoded protein. The changes in PRO994 expression, even if they are statistically significant, are at the level of nucleic acid, which is not necessarily correlated with protein expression or activity. Second, cDNA libraries have an inherent bias to them, therefore the results obtained in a cDNA library-based differential expression assay may not be representative of actual changes in the tissues from which the libraries are created. Ohara et al. (2001, Nucleic Acids Research 29(4):e22 p. 1 – 8, see especially Introduction) teach that cDNA libraries under-represent larger cDNAs and those that contain internal restriction sites. Further, the specification does not disclose the

biological significance of the changes in expression. Finally, the specification does not disclose whether the increase in PRO994 expression in rectal tumor, or the decrease of PRO994 expression in stomach tumor, is a cause of the tumors or a consequence of them. Since PRO994 expression increases in one tumor and decreases in another, its expression level cannot be considered as a marker for the presence or absence of a tumor. Therefore, there is no basis for the asserted use of the PRO994 protein or nucleic acid as a therapeutic target for treatment of the disease condition. Clearly, further research and experimentation are required to find out whether the PRO994 is useful as asserted.

A substantial utility, *by definition*, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In the instant case, the alterations in expression of PRO994 in stomach and rectum tumors (if significant), at the most, is an interesting invitation for further research, experimentation and confirmation as to whether the PRO994 polypeptide is useful as a diagnosis marker, or suitable as a therapeutic target for treatment of the tumors. These further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the claimed invention is not considered substantial.

Claims 1- 13 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Even if PRO994 had utility and were enabled, enablement would not be commensurate in scope with claims 1 - 5 because the specification does not reasonably provide enablement for polypeptides 80%, 85%, 90%, 95%, or 99% identical to SEQ ID NO:48. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731 737, 8 USPQ2d 1400 1404 (Fed. Cir. 1988).

The claims are directed to isolated polypeptides having at least 80% identity to a SEQ ID NO:48 with or without its signal peptide, or to polypeptides at least 80% identical to the extracellular domain of SEQ ID NO:48 with or without its signal peptide. Dependent claims are directed to chimeric polypeptides. The specification contains numerous asserted utilities including the identification of molecules that bind to PRO994 (including agonists and antagonists), as molecular weight markers, therapeutic agents, and for the production of antibodies. None of these asserted utilities is specific for the disclosed PRO994 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO994.

The specification of provisional application 60/090688 (p. 2, lines 18 – 20) teaches that the nucleic acid encoding PRO994 has (unspecified) homology to the nucleic acid which encodes the tumor associated-antigen L6, however the instant specification fails to indicate the degree of homology or whether the PRO994 has any homology thereto. There is disclosure of transmembrane domains (see particularly Figure 48), but no disclosure of any extracellular domain.

The Examiner has determined that polypeptides identical to PRO994 do not meet the utility requirements of 35 U.S.C. § 101, as detailed above. The claims encompass an unreasonable number of inoperative polypeptide sequences, which the skilled artisan would not know how to use. As opposed to the claims, what is disclosed about PRO994 is narrow: a single polypeptide with no utility.

There are no working examples of polypeptides less than 100% identical SEQ ID NO:47. There is only one function potentially attributed to nucleic acids encoding PRO994 (changes in expression in stomach and rectum tumors) but the examiner has determined that this is not sufficient to meet the requirements of 35 U.S.C. § 112, first paragraph, and furthermore there is no indication that the changes observed at the nucleic acid level are in fact reflected at the

protein level. While the specification generally describes properties of cytokines, it is acknowledged that cytokines are diverse in function and structure. The specification does not provide guidance for using polypeptides related to (i.e., 80%-99% identity) but not identical to SEQ ID NO:48, especially since the specification does not disclose any activity for PRO994.

The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation. An enabling description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO:48. Furthermore, protein function cannot be reliably predicted from sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance. Absent a clear disclosure of which elements of PRO994 are required for its activity, the claims to fusion proteins and variants that are related only by percentage of sequence identity are not fully enabled. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteins and lack of knowledge about functions of encompassed polypeptides structurally related to SEQ ID NO:48, the potential one limited working example of nucleic acid encoding PRO994 and its one asserted function, the lack of

direction or guidance for using either polypeptides that are not identical to SEQ ID NO:48, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

The examples provided in the specification do not provide a representative number of different amino acid sequences that would enable a representative number of the above discussed sequences with assurances that they possess the desired activity. The mere recitation of this term, and the definitions provided do not serve as sufficient guidance to enable the breadth of the claims for the various amino acid sequences claimed. See *Ex parte Forman*, 230 USPQ 546. Since the first paragraph of the statute under 35 U.S.C. § 112 requires that there must be an enabling disclosure to support the breadth of the claims, a review of the specification confirms that the scope of the various amino acid sequences that are discussed above have not been enabled. There is but a single amino acid disclosed with reference to PRO994, SEQ ID NO:48. In the absence of sufficient guidance, it would require undue experimentation to enable a commensurate number of the sequences that are encompassed by the claims.

Claims 1 – 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R § 1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 203018 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at least 30 years and *at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.* See 37 C.F.R. § 1.806.

Claims 1 – 5, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1 - 5 are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. Dependent claims 12 and 13 are drawn to chimeric polypeptides comprising sequences at least 80% identical to the disclosed sequence. The claims do not require that the claimed polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The specification of provisional application 60/090688 (p. 2, lines 18 – 20) teaches that the nucleic acid encoding PRO994 has (unspecified) homology to the nucleic acid which encodes the tumor associated-antigen L6, however the instant specification fails to indicate the degree of homology or whether the PRO994 protein has any homology thereto. The structure of the putative PRO994 peptide is disclosed as comprising four putative transmembrane domains at page 48 of the specification; however, it is clear from the disclosure that (a) only one of the four, if any, is likely to actually be a transmembrane domain, (b) if it is a transmembrane protein, which end of the protein would be the extracellular domain.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method

of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, polypeptides comprising the sequence of SEQ ID NO:48 or active or antigenic fragments thereof, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims that recite "the extracellular domain" of the protein are indefinite as no extracellular domain has been described. Therefore, the metes and bounds of the claims cannot be determined. For example, see Claim 1, parts (c) and (d). It is noted that four putative transmembrane domains are disclosed in Figure 48 of the specification; however, it is clear from the disclosure that there is no conception of whether PRO994 is in fact a transmembrane protein, and accordingly, which end of the protein would be the 'extracellular' domain. Further, as the protein is predicted to have four transmembrane domains (see Figure 48), it would be predicted to have more than one extracellular domain. Therefore the term "the extracellular domain" is indefinite as it is not clear to which extracellular domain applicant intends to refer. Finally, if the protein had a single extracellular domain, the recitation of "the extracellular domain. . .lacking its associated signal sequence" (claim 1, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHARON L. TURNER, PH.D.
PATENT EXAMINER
2-22-05

Daniel E. Kolker, Ph.D.

February 18, 2005